Remarks

There are no amendments to the claims. However, for ease of reference a complete listing of the claims follows the signature page of this response.

I. Addressing The Examiner's Rejections.

1. Rejection of Claims 87, 88, 90-96 and 98-114Under 35 U.S.C. §103(a).

The Examiner rejected claims 87, 88, 90-96 and 98-114 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Parker, et al., WO 00/40273, in view of Goeddel, et al., US 5,120,832, and further in view of Theeuwes, et al., US 4,976,966.

(A) The References Do Not Teach All of the Elements of the Claimed Invention.

To reject a claim based on combining prior art elements according to known methods to yield predictable results, the Examiner must resolve the Graham factual inquiries. *See Graham v. John Deere Co.*, 383 U.S. 1, 86 S. Ct. 684, 15 L Ed2d 545, 148 USPQ 459 (U.S. 1966). The Examiner must then articulate the following: (1) a finding that the prior art includes each element claimed with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination each element merely would have performed the same function as it did separately; (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. (*See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* 57526, 57529 Federal Register / Vol. 72, No. 195.)

The cited references do not teach all of the elements of the independent claims as presented in the accompanying amended claim set. Accordingly, a case of *prima facie* obviousness cannot be established.

First, none of the cited references teaches a method of treating hepatitis C (HCV) in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject (*see* independent claims 87, 88 and 114). The reference of Parker, et

al., teaches only the administration of a polynucleotide encoding an omega interferon (*see, e.g.,* Parker, et al., page 3, lines 2-4, lines 26-27, and page 5, lines 11-13). The Examiner asserts "[a]lthough Parker teaches administration of a polynucleotide encoding IFN-ω, a person of ordinary skill in the art would expect that this administered polynucleotide would be expressed and translated into IFN-ω protein, and that this polynucleotide-encoded IFN-ω protein would be effective in treating HCV infection" (*see* Office action, mailed 28 May 2008, page 4). This assertion is no more than a conclusionary statement for which the Examiner provides no supporting evidence. Essentially, the Examiner is equating treatment by administration of a protein to treatment using gene therapy. These two treatment methods are not equivalent. Administration of proteins for the treatment of disease is broadly used, for example, injection of insulin for the treatment of diabetes. However, administration of polynucleotide constructs in gene therapy methods to direct in vivo expression of therapeutic amounts of protein in a subject is rarely used in human subjects and is recognized in the art to be highly unpredictable.

In the accompanying Declaration Under 37 C.F.R. §1.132, Thomas R. Alessi, Ph.D. discusses limitations on the use of gene therapy for treatment of disease states. As the reference of the American Society of Gene Therapy (cited in the Declaration) clearly illustrates, gene therapy as of 2005 (about six years after the publication of the reference of Parker, et al.) was still in its infancy. There have not been clinical advances in application of gene therapy methods even to date. As stated in the Declaration:

> Accordingly, the Examiner's statement that "the polynucleotide of Parker would be expected to be expressed and translated into a therapeutically effective amount of IFN-ω, and this dose of IFN-ω would be expected to fall within the claimed dose ranges" (*see* Office action, mailed 28 May 2008, page 5) is completely unsubstantiated by the reference of Parker, et al. The Examiner has not provided any prior art supported evidence teaching predictable, sustained levels of protein expression in an animal subject using polynucleotide constructs. In fact, the Examiner's assertion of predictability appears to be contrary to the general state of the art of gene therapy as late as 2005, which is about six years after the publication of the reference of Parker, et al. (*See* Declaration Under 37 C.F.R. §1.132, paragraph #10.)

Further, the reference of Parker, et al., presents no data that demonstrate the usefulness of the administration of a polynucleotide encoding omega interferon for the

treatment of HCV. Example 6 of Parker, et al., is a prophetic example written in the present tense. The only virus shown by the reference to be affected by omega interferon is Murine Encephalomyocarditis Virus (EMCV) and only *in vitro* experimental data are given. No data related to *in vivo* treatment of any virus by administration of a polynucleotide encoding omega interferon to any animal is taught by the reference.

In the accompanying Declaration Under 37 C.F.R. §1.132, Thomas R. Alessi, Ph.D. discusses the fact that the Examiner has presented no scientific basis to support an extrapolation from the teachings of the reference of Parker, et al., concerning *in vitro* inhibition of EMCV to *in vivo* treatment of HCV in subjects as is claimed in the present application. Even alpha interferon has not been used and approved as a polynucleotide expression based treatment of HCV. As stated in the Declaration:

> Accordingly, even though the reference asserts an ability to treat HCV using a polynucleotide vector encoding omega interferon, the reference does not provide an enabling disclosure in this regard. I am not aware of any U.S. Food and Drug Administration (FDA) approved polynucleotide expression based treatment methods where the polynucleotide encodes alpha interferon. Further, I am not aware of any on-going clinical trials with such treatment. Treatment of chronic HCV infection with pegylated alpha interferon protein plus ribavirin is the current standard of care. (*See* Declaration Under 37 C.F.R. §1.132, paragraph #9.)

The reference of Goeddel, et al., also does not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject. The reference of Goeddel, et al., is discussed below.

Finally, the reference of Theeuwes, et al., does not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject.

Second, none of the cited references teaches or suggests the administration of omega interferon protein at the claimed microgram per week dosage ranges. The reference of Parker, et al., teaches only the administration of constructs comprising polynucleotides encoding omega interferon. It is notoriously difficult in the field of gene therapy in animals to control and maintain a predetermined range of expressed polypeptide over time from constructs comprising polynucleotides encoding polypeptides (*See* Declaration Under 37

C.F.R. §1.132, paragraph #10). Unpredictability associated with expression vectors, problems with innate immunity and tissue damage, problems with predictable gene expression and serious safety issues are generally recognized (*see, e.g.,* American Society of Gene Therapy, "Challenges in Advancing the Field of Gene Therapy: A Critical Review of the Science, Medicine, and Regulation" (*see* Declaration Under 37 C.F.R. §1.132, Appendix B)) as limiting the clinical success of gene therapy methods such as those disclosed by the reference of Parker, et al.

The Examiner suggests that "the general conditions of the invention are obvious in view of the prior art, it is not inventive to determine optimum or workable ranges by routine optimization" (*see* Office action, mailed 28 May 2008, pages 4-5). However, as discussed above "the general conditions of the invention" are not obvious in view of the prior art and the Examiner presents no evidence to support the assertion that the claimed ranges are nothing more than "routine optimization" particularly in view of the fact that no reference teaches treatment of HCV with omega interferon protein.

Further, HCV has been recalcitrant to treatment and even the most successful treatment method, prior to the methods of the present invention, using alpha interferon (with or without ribavirin) resulted in subjects having chronic HCV infection resistant to the treatment method (*see, e.g.,* the present specification, ¶0007; *see* also, Buckwold, et al., page 118, cols. 1-2; for a copy of Buckwold, et al., *see* Declaration Under 37 C.F.R. §1.132, Appendix B; Buckwold, et al., is also previously of record). As demonstrated in the present application, subjects having chronic HCV infection and even such subjects having chronic HCV infection resistant to treatment with alpha interferon (with or without ribavirin) show clearance of HCV in response to the treatment methods of the present invention (*see, e.g.,* specification, ¶0058-¶0059). In addition to the reference of Parker, et al., not addressing the claimed dosage ranges, neither of the secondary references teaches or suggests the administration of omega interferon protein at the claimed microgram per week dosage ranges.

The Examiner has not presented any evidence to support the assertion that one of ordinary skill in the art would predict that omega interferon is able to treat HCV infection in a subject in need of such treatment.

In the accompanying Declaration Under 37 C.F.R. §1.132, Thomas R. Alessi, Ph.D. discusses the limitations of the teachings of the reference of Goeddel, et al., including the Examiner's incorrect assumption that interferons are interchangeable in their pharmaceutical activities. In the Office action, mailed 28 May 2008, the Examiner asserts the following: "it is noted that Goeddel teaches that IFN-ω proteins exhibit biological activities, including antiviral activity that overlap with or are similar to other type I IFNs, such as IFN-α. Thus, one of ordinary skill in the art would expect that IFN-ω would exhibit anti-HCV activity in the same manner as IFN-α" (*see* Office action, mailed 28 May 2008, page 5). This assertion is unsupported by the Examiner and is inconsistent with what is known regarding omega interferon and interferons in general (*see* Declaration Under 37 C.F.R. §1.132, paragraph #11). In the Declaration, Dr. Alessi also discusses the very different physical and *in vitro* properties of omega interferon relative to alpha interferon (*See* Declaration Under 37 C.F.R. §1.132, paragraph #12).

Accordingly, the Examiner's extrapolation that, just because alpha interferon is used in the treatment of HCV, then one or ordinary skill in the art would with a reasonable degree of predictability know that omega interferon would provide a useful treatment of HCV, is unsubstantiated and incorrect.

In the accompanying Declaration, Dr. Alessi also discusses the reference of Viscomi (Appendix C of the Declaration) which teaches that omega interferon and alpha interferon show distinct properties and significant variety in their biological actions (*see* Declaration Under 37 C.F.R. §1.132, paragraph #13). Further, the reference of Buckwold, et al., points out several distinct differences between the antiviral activities of alpha, beta, gamma, and omega interferons (*see* Declaration Under 37 C.F.R. §1.132, paragraph #13). Thus, the Examiner's assertions regarding expectations of omega interferon to predictably perform the same as alpha interferon are merely conclusionary and not substantiated by any evidence.

The dependent claims distinguish over the combination of references by virtue of their incorporation of the limitations of the independent claim from which they depend.

Accordingly, Applicant submits that the Examiner has failed to establish a case of *prima facie* obviousness for the presently claimed invention as none of the cited references teaches the elements of the claimed invention. In view of the above-presented arguments,

Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

(B) The Primary Reference Teaches Away From the Claimed Invention.

Even if, for the sake of argument, the elements of the invention are taught by the prior art, obviousness cannot be established if the prior art teaches away from the claimed invention. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (57526, at 57529 Federal Register / Vol. 72, No. 195) state the following:

> Note that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. (Regarding "teaching away" the guidelines cite, *United States v. Adams*, 383 U.S. 39, 51–52, 148 USPQ 479, 483 (1966), wherein the Supreme Court would not require that one of ordinary skill in the art ignore the teaching away of the prior art.)

As discussed herein above, the primary reference of Parker, et al., teaches only the administration of a polynucleotide encoding an omega interferon (*See, e.g.,* Parker, et al., page 3, lines 2-4, lines 26-27, and page 5, lines 11-13). In fact, the reference of Parker, et al., notes that "IFN-omega has never been used for the treatment of infectious diseases, even in the form of a recombinant protein" (Parker, et al., page 2, lines 11-12; emphasis added). Further, the reference of Parker, et al., states "[T]reatment of infectious diseases with an interferon (IFN) has traditionally involved repeat injections of large doses of recombinant protein" (Parker, et al., page 1, lines 10-11). The reference goes on to state "[C]learly, there is a need for an improved delivery system for treating infectious diseases with IFNs." Following this introduction, all of the teachings of the reference of Parker, et al., are directed to the treatment of infectious disease by administering a polynucleotide construct into a tissue of a mammal and the advantages thereof. The reference does not teach a method involving administration of omega interferon protein nor any advantage to such a method.

A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *See, e.g., Bausch & Lomb v. Barnes-Hind/Hydrocurve*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). Prior art may be considered not to teach an invention, and thereby fail to support an obviousness rejection,

when the stated objectives of the prior art reinforce such an interpretation. *See, e.g., WMS Gaming Inc. v. International Game Tech*, 184 F.3d 1339, 51 USPQ2d 1385, 1400 (Fed. Cir. 1999). The stated objective of the reference of Parker, et al., is to provide an improved delivery system for treating infectious diseases with interferons wherein the system is the delivery of polynucleotides encoding omega interferon. Accordingly, the reference of Parker, et al., teaches away from the methods of the present invention that use administration of a therapeutically effective amount of omega interferon protein to a subject. Applicant submits that the Examiner's modification of the reference of Parker, et al., to achieve a contrary purpose to the stated objective of the reference is inappropriate and does not support a conclusion of obviousness. None of the cited secondary references makes up for this shortcoming of the reference of Parker, et al.

The dependent claims distinguish over the combination of references by virtue of their incorporation of the limitations of the independent claim from which they depend.

Accordingly, Applicant submits that the Examiner has failed to establish a case of *prima facie* obviousness for the presently claimed invention as modification of the reference of Parker, et al., along the lines suggested by the Examiner is counter to the stated intention of the reference. In view of the above-presented arguments, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

(C) Secondary Considerations.

In *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289; 82 USPQ2D 1385 (U.S. 2007), the Supreme Court reaffirmed use of the Graham factors in the determination of obviousness under 35 U.S.C. §103(a). The four factual inquiries under Graham are: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545, 148 USPQ 459, 467 (U.S. 1966).

The reference of Parker, et al., presents no data that demonstrate the effectiveness of the administration of a polynucleotide encoding omega interferon for the treatment of HCV.

The single example related to treatment of HCV is a prophetic example. In addition, as noted above, the reference of Parker, et al., does not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject. Applicant's specification teaches not only that administration of omega interferon protein is useful for the treatment of HCV infection (*see, e.g.,* specification ¶0059 and Figure 2) but also that administration of omega interferon protein is useful for the treatment of HCV infection in individual subjects with chronic HCV infection resistant to treatment with alpha interferon (with or without ribavirin). These advantages of the present invention were unrecognized in the prior art. In addition, as stated by the later published reference of Buckwold, et al., treatment of subjects with omega interferon protein is well tolerated (*see, e.g.,* Abstract and page 119, col. 1, first full paragraph). This presents another advantage of the treatment method of the present invention.

In the Office action, the Examiner asserts "because the combination of Parker and Goeddel suggest treatment of HCV infection by administration of IFN-ω proteins, a person of ordinary skill in the art would be motivated to administer IFN-ω in cases where IFN-α has not been effective" (*see* Office action, mailed 28 May 2008, pages 5-6). The Examiner has presented no evidence to support this assertion. Further, the assertion makes no logical sense in the context of the Examiner's assertion that "Goeddel teaches that IFN-ω proteins exhibit biological activities, including antiviral activity that overlap with or are similar to other type I IFNs, such as IFN-α. Thus, one of ordinary skill in the art would expect that IFN-ω would exhibit anti-HCV activity in the **same manner** as IFN-α." (*See* Office action, mailed 28 May 2008, page 5; emphasis added.) If, for the sake of argument, two interferons act in "the same manner"' then why would one work in a treatment method when the other one did not? The Examiner's assertions are incompatible and neither is supported by teachings of the cited references. In the accompanying Declaration Under 37 C.F.R. §1.132, Dr. Alessi presents arguments against omega interferon and alpha interferon having equivalent pharmaceutical activity, including teachings of the present specification that disclose successful treatment of human patients with omega interferon who failed treatment using alpha interferon (*see* Declaration Under 37 C.F.R. §1.132, paragraph #14).

Further, as stated in the reference of Buckwold, et al., "[O]ther antiviral therapies to

treat HCV-infected patients are desperately needed" (page 118, col. 2). The present invention provides such antiviral therapy and the methods of treatment disclosed in the present specification are consistent with the teachings of the reference of Buckwold, et al., concerning the antiviral activity of omega interferon against HCV.

In the accompanying Declaration Under 37 C.F.R. §1.132, Dr. Alessi discusses that he was involved in working on the therapeutic applications of alpha interferon, in particular treatment of HCV infection using interferon alfa-2b. Dr. Alessi points out that omega interferon has been known to one of ordinary skill in the art since the mid-1980's yet, prior to the work at Intarcia Therapeutics, Inc., there was no interest in the use of omega interferon protein for the treatment of HCV infection (*see* Declaration Under 37 C.F.R. §1.132, paragraph #16).

In the Office action, the Examiner asserts the following:

> ... in the absence of evidence to the contrary, the polynucleotide of Parker would be expected to be translated into a therapeutically effective amount of IFN-ω, and this dose of IFN-ω would be expected to fall within the claimed dose ranges, otherwise the treatment of Parker would not be effective. Thus, without a clear showing that expression of the polynucleotide of Parker in a subject in need would not produce serum levels of IFN-ω protein within the claimed dosage ranges, one of ordinary skill in the art would assume that the IFN-ω translated from Parker's polynucleotide would meet the limitations of the claims. (*See* Office action, mailed 28 May 2008, page 5.)

First, the Examiner has only asserted and has not presented any evidence to support that "this dose of IFN-ω would be expected to fall within the claimed dose ranges." Applicant on the other hand has provided evidence concerning the unpredictability of gene therapy methods. Second, there is no enabling support in the reference of Parker, et al., to show that the treatment method proposed by Parker, et al., would be effective for *in vivo* treatment of HCV infection in subjects. The reference of Parker, et al., is a published PCT International Application that was never, to the best of Applicant's knowledge, examined by any recognized national examining office. Published PCT International Applications are not peer reviewed. Accordingly, there is no presumption of validity of any kind associated with the Parker, et al., reference. Finally, the Examiner asserts "without a clear showing that expression of the polynucleotide of Parker in a subject in need would not produce serum

levels of IFN-ω protein within the claimed dosage ranges ... one of ordinary skill in the art would assume that the IFN-ω translated from Parker's polynucleotide would meet the limitations of the claims." Is the Examiner suggesting Applicant undertake clinical gene therapy trials to produce such a showing? In view of the state of gene therapy and the complexity and cost of such a gene therapy trial, this is not a feasible or realistic suggestion nor is it legally required.

In the Declaration, Dr. Alessi discusses the actual clinical work that has been and continues to be conducted by Intarcia Therapeutics, Inc., proving the value and usefulness of treatment of HCV using omega interferon protein by injection and by using implantable osmotic delivery systems to deliver omega interferon protein continuously over extended time periods (*see* Declaration Under 37 C.F.R. §1.132, paragraph #15).

Accordingly, these unappreciated and unexpected advantages of the present invention should be evaluated in the context of any asserted rejection under 35 U.S.C. §103(a). Applicant submits that the Examiner has not addressed these secondary considerations and respectfully requests their consideration.

(D) Opinion of Dr. Alessi as one of ordinary skill in the art.

Finally, in paragraph #17 of the Declaration, Dr. Alessi further provides his opinion as one who has worked in and is familiar with the art of therapeutic uses of interferons that:

- in the absence of any prior *in vitro* data and in particular in the absence of clinical data on the usefulness of the administration of omega interferon protein for the treatment of HCV, any assertion of the probable efficacy of such treatment based on the cited references is no more than wishful thinking;
- the references cited by the Examiner do not support a finding that a typical scientist at the time the invention was made would have assumed that administration of omega interferon protein would be efficacious for the treatment of HCV based on the assertion of the Parker, et al., reference that a polynucleotide encoding omega interferon might be used to treat HCV;
- the references do not support a finding that a typical scientist at the time the invention was made would assume that omega interferon protein would be expected to perform

all the same functions as alpha interferon;

- the references do not support a finding that a typical scientist at the time the invention was made would be motivated (*see, e.g.,* Office action, mailed 28 May 2008, page 4 and page 6) to administer omega interferon protein for the treatment of HCV rather than the standard of treatment of alpha interferon protein; and
- the references do not support a finding that a typical scientist at the time the invention was made would have recognized that the HCV treatment results obtained by the claimed methods were predictable.

As discussed herein above and in the Declaration, the Examiner has not provided evidence to support the Examiner's assertion that the presently claimed invention is obvious over the combination of Parker, et al., WO 00/40273, in view of Goeddel, et al., US 5,120,832, and further in view of Theeuwes, et al., US 4,976,966. In view of the above-arguments and the Declaration Under 37 C.F.R. §1.132 by Dr. Alessi, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of the rejection of the claims under 35 U.S.C. §103.

2. Rejection of Claims 87, 98, 103 and 109-113 Under 35 U.S.C. §103(a).

The Examiner rejected claims 87, 98, 103 and 109-113 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Parker, et al., WO 00/40273, in view of Goeddel, et al., US 5,120,832, and further in view of Theeuwes, et al., US 4,976,966, and Guillen, et al., US 6,074,673.

The combination of references, as discussed herein above, does not teach all of the elements of the claimed invention. The addition of the reference of Guillen, et al., to the references cited in the previous rejection does not make up for any of the shortcomings of the cited references as discussed herein above. The reference of Guillen, et al., does not teach omega interferon protein nor does it teach treatment of HCV. As noted by the Examiner, the "Guillen *et al.* reference was included in the rejection to teach kits" (*see* Office action, mailed 28 May 2008, page 7).

In order for a combination of references to render obvious a claimed invention, all of

the recited elements of claimed invention must be taught by the combination of references. Further, the combination of references does not render the presently claimed invention obvious because the primary reference teaches away from the present invention as discussed herein above. Accordingly, the Examiner has failed to establish a case of *prima facie* obviousness for independent claims 87, 88 and 114. The dependent claims distinguish over the combination of references by virtue of their incorporation of the limitations of the independent claim from which they depend.

Accordingly, applicant submits that the Examiner has failed to establish a case of *prima facie* obviousness. In view of the above-presented arguments, applicant respectfully requests that the rejections under 35 U.S.C. §103 be withdrawn.

3. Provisional Non-Statutory Obviousness-Type Double Patenting Rejections.

The Examiner provisionally rejected claims 87, 88, 90-96, 98-108 and 114 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 65 and 86-104 of co-pending Application No. 10/982,532.

The Examiner provisionally rejected claims 87, 88, 90-96, 98-108 and 114 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 5-7, 17-22, 25 and 40-55 of co-pending Application No. 11/811,415.

As these are both provisional obviousness-type double patenting rejections and because no conflicting claims have been patented, Applicant respectfully requests that the provisional rejections be held in abeyance until agreement on allowable subject matter is established in the present application. Applicant notes that co-pending Application Nos. 10/982,532 and 11/811,415 are both commonly owned with the present application by Intarcia Therapeutics, Inc.

II. Conclusion.

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art.

Please direct all further communications in this application to:

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If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 780-9030.

Respectfully submitted,

Dated: 27 October 2008 By : Gary R Fabian

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